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* APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,984	09/25/2000	Donn Nelton Rubingh	7070	3865

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,984	RUBINGH ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 11-28* is/are pending in the application.

4a) Of the above claim(s) *17,19,23,25 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11-16,18,20-22,24,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

Applicant's Amendment C, Paper No. 16 filed February 24, 2003, has been entered, together with the accompanying Terminal Disclaimer which is effective in avoiding the nonstatutory double patenting rejection of claims 1, 2, 11-16, 18, 20, 21, 24 and 26 herein over claims in the copending application 09/618,845, allowed on March 3, 2003. The amendments to claims 1 and 12-14 presented in Paper No. 16 do not, however, overcome the rejections of record of claims 1, 2, 11-16, 18, 20-22, 24, 26 and 27 herein under the second paragraph of 35 U.S.C. §112 and 35 U.S.C. §103(a) for the reasons set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and 11-16, 18, 20-22, 24, 26 and 27 are rejected, essentially for reasons of record, under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed February 24, 2003, have been fully considered but they are not persuasive because the amendments to claim 1 and 12-14 are incomplete. Applicant's amendments necessitate the restatement of the rejection of record. Claim 1 remains indefinite in reciting, at lines 1-4, "[a] variant [. . . that] comprises a deletion of an amino acid at one or more of positions 70-84 **corresponding to subtilisin BPN'**" and this same recitation also occurs in claim 24. Yet the specification indicates that Applicant does not intend that this range of recited positions correspond to the entire sequence of the mature subtilisin BPN' protease. This is meaningless and would not permit the claim to extend to other subtilisins according to claim 2. Applicant instead intended that deletions of the invention be made in subtilisins generally and occur **at positions that correspond to**

one or more of positions 70-84 of the amino acid sequence of subtilisin BPN'. Claims 2, 11 and 18, 20-22, 24, 26 and 27 - particularly claim 24 - are included in this rejection of claim 1 because they fail to clarify the ambiguity of the claim from which they depend.

Claims 12-14 are indefinite in reciting, "deletion of an amino acid at one or more of positions . . . corresponding to subtilisin BPN'", but claims 12-14 all depend from claim 11 which limits claim 1 to deletions particularly in subtilisin BPN' thus the deletions cannot "correspond" to deletions at certain positions in the amino acid sequence of subtilisin BPN' because they are in the amino acid sequence of subtilisin BPN'. The terminal phrase of each claim would therefore logically recite, "in the amino acid sequence of subtilisin BPN'". Claims 15 and 16 are included in this rejection of claim 13 because they fail to clarify the ambiguity of the claim from which they depend.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 1, 2, 11-20, 22, 23, and 27 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bryan et al., U.S. Patent No. 5,567,601, of record.

While this is essentially the rejection of record, claim 27, previously omitted, is now included. Therefore the rejection differs from that stated in Paper No. 14 mailed October 22, 2002. Applicant's arguments filed February 24, 2003, have been fully considered

but they are not persuasive. Applicant suggests at pages 2-3 of Paper No. 16 that the teachings of Bryan et al. are inapplicable due to the absence of a specific exemplification by Bryan et al. in their patent of subtilisin BPN' mutants that, according to the clear teaching of Bryan et al. at the close of col. 4, "comprise one or more" deletions "of the amino acids at positions 75-83" in addition to their "most preferred" deletion "of amino acids 75-83, of SEQUENCE ID NO:1". Bryan et al. was not cited as an anticipatory reference, yet comparison of claim 1 of Bryan et al. and the teachings at col. 4 of Bryan et al. with claim 1 herein shows that Bryan et al. intend to claim amino acid deletions beyond their "most preferred deletion" at positions that correspond to positions in the amino acid sequence of subtilisin BPN' such as those itemized in clauses (a) through (j) of claim 15, as well as paired deletions such as Δ70, 71; Δ70, 76; Δ75, 74; Δ75, 76; etc., and further triple, quadruple, quintuple, and other multiple, deletions. Applicant has not presented claims that specifically recite further deletions embraced by claim 1 herein, and has not specifically exemplified such further deletions in the instant specification, but the absence of a specific exemplification does not detract from Applicants' teachings any more than lack of specific examples of the deletions taught by Bryan et al. detracts from the ability of their teachings to guide and motivate one of ordinary skill in the art at the time the invention was made to make the further deletions they teach.

Bryan et al. explicitly teach that partial or total deletion of the amino acids at positions that contribute to the primary calcium binding site, comprised by amino acid positions 75-83 of subtilisin BPN', as well as similar deletions at corresponding amino acid positions in other subtilisins will reduce the binding affinity for calcium ion. This constitutes both guidance and motivation for one of ordinary skill in the art at the time the invention of made to make the other deletions taught by Bryan et al., but not specifically exemplified, because the artisan would have a reasonable expectation of the positive outcome taught by

Bryan et al. The further teaching of Bryan et al., col. 11 at lines 36-41 and claim 1, lines 7-15, that "one or more additional" deletions of amino acids at "the α-helix amino acid positions 70-74" may be included in a subtilisin mutant together with the deletions of one or more amino acids at the positions corresponding to positions 75-83 of subtilisin BPN' similarly constitutes guidance and motivation for one of ordinary skill in the art at the time the invention of made to make further deletions taught by Bryan et al., but not specifically exemplified, because the artisan would, again, have had a reasonable expectation of success in achieving the worthwhile results taught by Bryan et al. Further, claim 1 of Bryan et al. further embraces, and claims 2-6 and 11 particularly specify, other "stabilizing, mutations compris[e] amino acid . . . substitutions . . . at . . . the ß-ribbon amino acid positions 202-219." Thus Bryan et al. teach the preparation of stabilizing amino acid substitutions claimed herein, a number of which they had introduced to compensate for the reduced thermal stability of the subtilisin mutants lacking one or more of the native amino acids at positions corresponding to positions 70-83 of subtilisin BPN'. Bryan et al. teach that their subtilisin BPN' mutants should be used in detergent compositions, which are cleaning compositions, designed for use with water having a low concentration of calcium ion. Claim 27 herein is also rejected because Bryan et al. teach the preparation of nucleic acid sequences encoding their altered subtilisins, hence "mutant genes", see claims 13 and 14 of Bryan et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin mutant gene that encodes a subtilisin variant of claim 1 in order to produce it recombinantly as Bryan et al. had with their variants.

Applicant presents a corollary argument at pages 3 and 4 of Paper No. 16, asserting that different reasons motivated Applicant and Bryan et al. to make amino acid sequence deletions at the same subtilisin BPN'-correspondent positions 70-84 and that such different motivations should somehow alter the analysis of obviousness under 35 U.S.C. §103(a).

This outlook is mistaken because the artisan need only find that the teachings of the prior art provide sufficient motivation to make a claimed invention, not a motivation identical to that of a subsequent applicant for patent. One of ordinary skill in the art at the time the invention was made is considered to have had a reasonable expectation that following the guidance of Bryan et al. would produce subtilisin variants, in addition to their "most preferred variant", that are less dependent on calcium ion for stability yet have adequate stability by incorporating the series of stabilizing deletions and/or substitutions at positions that Bryan et al. teach should be included when altering the calcium binding site region. It is again noted that no pending claim currently requires that a subtilisin variant have a deletion of the amino acid at the position that corresponds to the subtilisin BPN' position 84. This is the only site for deletions claimed herein not taught by Bryan et al. to be a worthwhile site for an amino acid deletion in a subtilisin amino acid sequence among the subtilisin BPN'-correspondent positions 70-84. The rejection of record is maintained.

Claims 24 and 26 are for reasons of record rejected under 35 U.S.C. §103(a) as being unpatentable over Bryan et al. as applied to claims 1, 2, 11-20, 22, 23, 27, and 28 above, and further in view of Powell et al., U.S. Patent No. 6,060,546, of record.

Applicant's arguments filed February 24, 2003, have been fully considered but they are not persuasive. The teachings of Bryan et al. discussed above are taken as before. Applicant suggests that the teachings of Bryan et al. of making amino acid deletion and substitution mutations in subtilisins to make variants more stable, thus more useful, water having a low concentration of calcium ion might inappropriately have been combined with teachings of Powell et al. of the use of a serine protease in a personal care composition. Yet the term "personal care composition" embraces many cleansing compositions wherein metal chelators may be present, or formulated with soft water, such as shampoos and skin cleansers. Applicant provides no reason why one of ordinary skill in the art at that time would have expected that subtilisin variants suggested by Bryan et al. might be unsuitable

for incorporation in personal care compositions, particularly when destined for use with "soft" water or in a solution with a low calcium ion concentration such as the non-aqueous solution of Powell et al., where the artisan would have had a reasonable expectation, on the basis of the teachings of Bryan et al., that it would exhibit better stability than the native protease taught by Powell et al. The rejection of record is maintained.

Claim 21 remains rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over Bryan et al. as applied to claims 1, 2, 11-20, 22, 23, 27, and 28 above, and further in view of Arbige et al., EP 0 260 105, of record.

Applicant's arguments filed February 24, 2003, have been fully considered but they are not persuasive. The teachings of Bryan et al. discussed above are taken as before. Applicant suggests that a prior teaching of a stabilizing substitution at the subtilisin BPN'-correspondent position 217 that differs from the stabilizing substitution Bryan et al. made at the same position might be inappropriately applied because the medium in which stabilization is desired differs, i.e., that Arbige et al. teach that making the substitution Y217L in subtilisin BPN', see page 6, line 46, through page 7, line 27, produces a mutant having increased stability and activity by comparison with the native subtilisin BPN' in non-aqueous solutions. Yet Bryan et al. teach that amino acid substitutions may be made at this same subtilisin BPN'-correspondent position, see claims 1-8, and in subtilisin BPN' at position 217 to stabilize the resulting variant. Applicant presents no compelling reason why one of ordinary skill in the art at the time the invention was made would have considered both the Y217K and Y217L stabilizing substitutions in the prior art to both be advantageous where both Arbige et al. and Bryan et al. teach that their substitutions for the tyrosine at a position corresponding to position 217 in the amino acid sequence of subtilisin BPN' produces a more stable variant in solution conditions where calcium ion concentrations are low to non-existent and such an artisan at that time would have had a reasonable expectation that a Y217L-substituted calcium binding region deletion mutant

would exhibit a stability comparable at least to a Y217K-substituted calcium binding region deletion mutant. The rejection of record is maintained.

Conclusion

No claim is allowed. It is noted that claims 17, 19, 23, 25 and 28 remain in the application although they were withdrawn from further consideration as being drawn to a non-elected invention in Paper No. 14.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
May 14, 2003